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ORIGINAL RESEARCH

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Treatment outcomes and survival in morbidly obese women with endometrial cancer

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Abstract

Background: Morbid obesity presents a challenge in providing standard treatment in endometrial cancer (EC). We aim to evaluate the impact of morbid obesity on treatment and survival outcomes in women with EC. **Methods**: Patients diagnosed with EC from 2005–2015 were stratified by body mass index (BMI $\geq$40 kg/m^2 *vs.* $<$40 kg/m^2) and low risk (LR) and high risk (HR) subgroups based on stage, grade, myometrial invasion and histology. Demographics, tumor characteristics and treatment-related outcomes were analyzed. Univariate, multivariable and propensity-weighted Cox models were used to evaluate progression free survival (PFS) and overall survival (OS). **Results**: Of 1778 evaluable patients, those with BMI $\geq$40 kg/m^2 were significantly younger, more likely endometrioid histology, lower grade, earlier stage, myometrial invasion $<$50% and absent lymph-vascular space invasion (LVSI). A similar proportion of patients with BMI $<$40 and $\geq$40 kg/m^2 in LR and HR groups received radiation and chemotherapy. However, morbidly obese patients were less likely to undergo lymphadenectomy in both risk groups (p = 0.012 and p = 0.009, respectively). On propensity-weighted analysis, there was no significant difference in PFS or OS between patients with BMI $<$40 and $\geq$40 kg/m^2 (HR 0.89, 95% CI (confidence interval) (0.60, 1.30) and HR 0.74, 95% CI (0.49, 1.12) respectively). **Conclusions**: Morbid obesity is associated with favorable prognostic factors in EC patients. When stratified by risk group, morbidly obese patients receive similar postoperative treatment but are less likely to undergo lymphadenectomy. PFS and OS are similar between patients with BMI $<$40 and $\geq$40 kg/m^2 when risk groups and propensity score matching are considered.

Keywords

Endometrial neoplasms; Obesity; Survival; Uterine neoplasms

1. Introduction

Obesity, defined as a body mass index greater than 30 kg/m^2, is a major public health concern, with over one-third of United States adults categorized as obese, and a doubling of obesity rates world-wide in the last thirty years [1, 2]. Obesity is a well-known risk factor for endometrial cancer. There is an increase in relative risk for endometrial cancer of 60% per 5 kg/m^2 higher body mass index or BMI [3–5]. Endometrial cancer cases have drastically increased over the last decades in parallel with the rise in obesity with an approximate 1% increase per year over the last 10 years. Additionally, an increase in endometrial cancer death rate by an average of 1.5% each year has been observed [6]. While obesity has clearly been associated with increased risk of development of endometrial cancer, data assessing the impact of morbid obesity on survival outcomes are conflicting.

Several studies have found an inverse correlation between obesity and survival. Systematic reviews and meta-analyses show higher odds of all-cause mortality with increasing BMI in endometrial cancer patients. For example, Secord *et al.* [7] indicated that a 10% increase in BMI resulted in a 9.2% increase in the likelihood of all-cause mortality. Von Gruenigen *et al.* [8] found that an incremental increase in BMI was associated with increased likelihood of mortality, with the highest mortality rate in the BMI $\geq$40 kg/m^2 group [4, 7–10]. In contrast, other studies have found no effect or even a favorable prognosis in obese endometrial cancer patients, presumably due to presence of clinical markers of less aggressive disease [11–15]. A study by Van Arsdale found that obesity (BMI $>$35 kg/m^2) is associated with improved disease-specific survival, particularly in patients with advanced non-endometrioid type endometrial cancers [15].

While data on survival outcomes for obese patients with EC are contradictory, clinical challenges are often encountered in the treatment of medically higher risk morbidly obese patients, which leads to concerns regarding adverse effects of obesity in cancer care. Obesity is known to be associated with many adverse health complications, including type 2 diabetes, hypertension, heart disease and stroke, which are primary drivers

of worse overall survival in this patient population. Other hypotheses regarding adverse effects in treatment include surgical morbidity, altered pharmacokinetics with chemotherapy dosing, and decreased efficacy with staging procedures leading to under-treatment of occult advanced disease [16–19]. Although early stage endometrial cancer generally has an excellent prognosis, with a 5-year survival of over 80% for all-comers and 95% for localized disease [6], it is unclear how survival is impacted by suboptimal surgical treatment, staging and adjuvant therapy. In this study, we evaluate the impact of morbid obesity on surgical and disease-specific outcomes and adjuvant treatment use in women with low risk and high-risk endometrial cancer.

2. Materials and methods

All patients diagnosed with endometrial carcinoma treated at the Cleveland Clinic from 01 January 2005 through 30 December 2015 were retrospectively reviewed after approval obtained from the Institutional Review Board. All patients were included regardless of treatment received. Nonsurgical patients were included given concern that morbidly obese patients may be treated with discrepant nonsurgical therapy to avoid increased operative risk. Patients were stratified by BMI (control group <40 kg/m^2 or morbidly obese group ≥ 40 kg/m^2). Associations between treatment provided and survival outcomes were assessed in low risk and high-risk subgroups. Risk groups were defined as (1) low risk (LR) meeting all four following criteria: stage 1–2, low or moderate grade, $<50\%$ myometrial invasion and endometrioid type, and (2) high risk (HR) meeting at least one of the following criteria: stage 3–4, high grade, $\geq 50\%$ myometrial invasion or non-endometrioid type. Stage and myometrial invasion were obtained from our institutional database and were individually verified via pathology reports for dates 01 January 2008 to 01 January 2011 to account for change in FIGO (International Federation of Gynecology and Oncology) staging in 2009. Demographic and pathologic variables were evaluated including age at diagnosis, race, primary payer at diagnosis, histology, grade, any lymph-vascular space invasion (LVSI), and tumor size. Treatment variables including surgery (defined as at least hysterectomy with or without bilateral salpingo-oophorectomy), performance of lymphadenectomy and receipt of adjuvant chemotherapy or radiation therapy were collected. All variables were compared between control and morbidly obese patients overall and after stratification into LR and HR groups. Progression free survival (PFS) and overall survival (OS) outcomes were reported.

Statistical analysis incorporated Pearson chi-square test or Fisher's exact test for categorical factors, and two-sample *t*-test or Wilcoxon rank sum test for continuous factors. For survival analysis, starting dates were set to be the diagnosis date. For progression free survival, those patients that never achieved remission were set to have the event at day zero. Survival year was defined as 365.25 days, and both PFS and OS were censored at 6 years. Cox proportional hazards regression right-censored univariate and multivariable models were fit for PFS and OS. Kaplan-Meier survival curves were created for both risk subgroups. Furthermore, propensity analysis with inverse probability of treatment weighting was performed to estimate the average causal effect of morbid obesity on survival compared to the control (*i.e.*, Average Treatment Effects on the Treated (ATT), in which we regarded morbidly obese group as the treated). The propensity model included demographics and treatment variables, which included age, race, insurance status, grade, stage, treatment and risk group. Propensity-weighted Cox models using ATT weights were performed for PFS and OS. We planned to additionally control any variables that had propensity-weighted standardized mean differences exceeding 0.25 or 0.10 with absolute differences above 0.05. All analyses were done using SAS (version 9.4, The SAS Institute, Cary, NC, USA) and a $p < 0.05$ was considered statistically significant.

3. Results

Of 2394 patients assessed for eligibility, 1778 patients were included in the study. Reasons for exclusion were: final pathology diagnosis of endometrial hyperplasia, unknown BMI or incomplete data (Fig. 1). Of the 1778 patients included in the study, 1331 (74.9%) had a BMI <40 kg/m^2 and 447 (25.1%) were ≥ 40 kg/m^2. Patients with BMI ≥ 40 kg/m^2 were significantly younger (58.9 ± 10 *vs.* 64.2 ± 11 years, $p < 0.001$), more likely to have endometrioid histology (77.6% *vs.* 66.9%, $p < 0.001$), lower FIGO grade (52.6% *vs.* 37.9% grade 1, $p < 0.001$), earlier stage (77.4% *vs.* 66.4% stage 1, $p < 0.001$), myometrial invasion $<50\%$ (66% *vs.* 50.1%, $p < 0.001$) and absent LVSI (48.5% *vs.* 39.1%, $p < 0.001$). Patients in both BMI groups (≥ 40 kg/m^2 and <40 kg/m^2) underwent surgery in nearly all cases (96.4% *vs.* 96.8%), and the remaining patients underwent non-surgical treatment. However, morbidly obese patients were significantly less likely to undergo lymphadenectomy (43.6% *vs.* 60%, $p < 0.001$). Treatment modalities differed between groups, with morbidly obese patients receiving less radiation therapy (31.5% *vs.* 43.5%, $p < 0.001$), and less chemotherapy (22.4% *vs.* 31.3%, $p < 0.001$) (Table 1).

When stratified by risk group, patients with BMI ≥ 40 kg/m^2 comprised 32.6% of LR risk group, and were more likely to be younger (57.5 ± 9.5 *vs.* 61.4 ± 10.9 years, $p < 0.001$), of African American race (10.3% *vs.* 4.4%, $p = 0.003$), and uninsured (18.6% *vs.* 12.8%, $p = 0.045$). In the LR group, morbidly obese patients had similar rates of LVSI and similar tumor size compared to those with BMI <40 kg/m^2 (**Supplementary Table 1**). All patients in the LR group received surgery. Overall, 37.2% of LR patients underwent lymphadenectomy. However, compared to patients with BMI <40 kg/m^2, those with BMI ≥ 40 kg/m^2 in the LR group were significantly less likely to undergo lymphadenectomy (30% *vs.* 40.7%, $p = 0.012$). Median number of lymph nodes removed was similar between groups. The rate of administration of adjuvant radiation and chemotherapy was similar between both risk groups (Table 2).

Within the HR group, 19.4% of patients had BMI ≥ 40 kg/m^2. Patients with BMI ≥ 40 kg/m^2 were more likely to be younger (60.6 ± 10.3 *vs.* 66 ± 10.9 years, $p < 0.001$), though with similar race, insurance status, histology, grade, stage, myometrial invasion, LVSI status and tumor size to those with BMI <40 kg/m^2 (**Supplementary Table 2**). Surgery

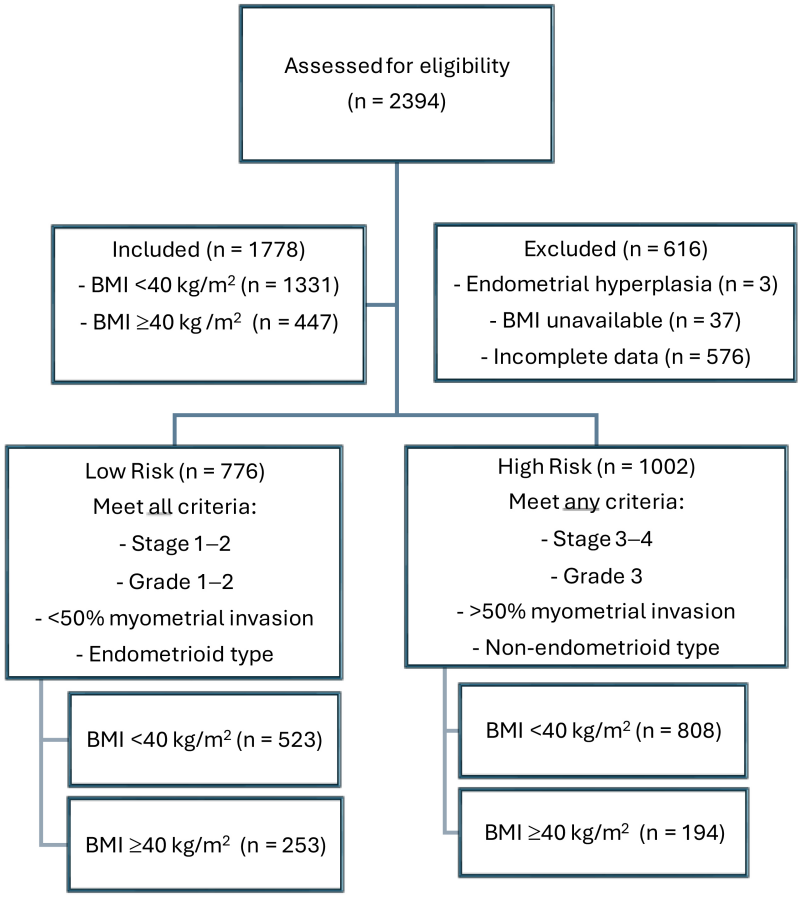

FIGURE 1. Cohort selection. Flowchart indicating candidates eligible for study, excluded cases and patients included divided into BMI $<$ or $\geq$40 kg/m^2, then further divided into low risk and high risk categories. BMI: body mass index.

TABLE 1. Demographic, clinical characteristics and treatment by BMI group.

Factor	Total (N = 1778)	BMI <40 kg/m^2 (N = 1331)	BMI ≥40 kg/m^2 (N = 447)	*p*-value
Age at diagnosis (yr)*	62.9 ± 11.1	64.2 ± 11.1	58.9 ± 10.0	<0.001[a]
Race				
White	1577 (88.7)	1180 (88.7)	397 (88.8)	
Black	165 (9.3)	118 (8.9)	47 (10.5)	
Asian	11 (0.62)	11 (0.83)	0 (0.00)	0.130[d]
American Indian	2 (0.11)	2 (0.15)	0 (0.00)	
Other/Unknown	23 (1.30)	20 (1.50)	3 (0.67)	
Race*				
White	1577 (88.7)	1180 (88.7)	397 (88.8)	
Black	165 (9.3)	118 (8.9)	47 (10.5)	0.041[c]
Other/Unknown	36 (2.00)	33 (2.50)	3 (0.67)	
Primary payer at diagnosis*				
No insurance/Unknown	260 (14.6)	188 (14.1)	72 (16.1)	
Medicare/Medicaid/Veterans affairs	638 (35.9)	501 (37.6)	137 (30.6)	0.049[c]
Private insurance	767 (43.1)	556 (41.8)	211 (47.2)	
Insured, NOS	113 (6.4)	86 (6.5)	27 (6.0)	
Risk group*				
Low risk	776 (43.6)	523 (39.3)	253 (56.6)	<0.001[c]
High risk	1002 (56.4)	808 (60.7)	194 (43.4)	

TABLE 1. Continued.

Factor	Total (N = 1778)	BMI <40 kg/m^2 (N = 1331)	BMI ≥40 kg/m^2 (N = 447)	*p*-value
Histology*				
Endometroid	1237 (69.6)	890 (66.9)	347 (77.6)	
Unknown	76 (4.3)	65 (4.9)	11 (2.5)	<0.001[c]
Others	465 (26.2)	376 (28.2)	89 (19.9)	
Grade of differentiation*				
Well differentiated	739 (41.6)	504 (37.9)	235 (52.6)	
Moderately differentiated	466 (26.2)	365 (27.4)	101 (22.6)	<0.001[c]
Poorly differentiated	573 (32.2)	462 (34.7)	111 (24.8)	
FIGO stage				
I	1230 (69.2)	884 (66.4)	346 (77.4)	
II	115 (6.5)	90 (6.8)	25 (5.6)	
III	277 (15.6)	225 (16.9)	52 (11.6)	<0.001[c]
IV	107 (6.0)	89 (6.7)	18 (4.0)	
Unknown	49 (2.8)	43 (3.2)	6 (1.3)	
FIGO stage*				
I/II	1345 (75.6)	974 (73.2)	371 (83.0)	
III/IV	384 (21.6)	314 (23.6)	70 (15.7)	<0.001[c]
UNK	49 (2.8)	43 (3.2)	6 (1.3)	
Myometrial invasion*				
<50%	962 (54.1)	667 (50.1)	295 (66.0)	
≥50%	215 (12.1)	178 (13.4)	37 (8.3)	<0.001[c]
Unknown	601 (33.8)	486 (36.5)	115 (25.7)	
LVSI*				
No	738 (41.5)	521 (39.1)	217 (48.5)	
Yes	350 (19.7)	285 (21.4)	65 (14.5)	<0.001[c]
Unknown	690 (38.8)	525 (39.4)	165 (36.9)	
Tumor size*				
<2 cm	296 (16.6)	219 (16.5)	77 (17.2)	
≥2 cm	1147 (64.5)	869 (65.3)	278 (62.2)	0.450[c]
Unknown	335 (18.8)	243 (18.3)	92 (20.6)	
Surgery done (at least hysterectomy)*				
No	59 (3.3)	43 (3.2)	16 (3.6)	0.720[c]
Yes	1719 (96.7)	1288 (96.8)	431 (96.4)	
Lymphadenectomy*				
No	745 (41.9)	506 (38.0)	239 (53.5)	
Yes	994 (55.9)	799 (60.0)	195 (43.6)	<0.001[c]
Unknown	39 (2.2)	26 (2.0)	13 (2.9)	
Number of lymph nodes removed**	19.0 [12.0, 27.0]	19.0 [12.0, 27.0]	19.0 [11.0, 27.0]	0.720[b]
Radiation				
None	1058 (59.5)	752 (56.5)	306 (68.5)	
Brachytherapy only	175 (9.8)	143 (10.7)	32 (7.2)	<0.001[c]
External beam radiation therapy	456 (25.6)	360 (27.0)	96 (21.5)	
Other/Unknown	89 (5.0)	76 (5.7)	13 (2.9)	
Any radiation therapy*				
No	1058 (59.5)	752 (56.5)	306 (68.5)	<0.001[c]
Yes	720 (40.5)	579 (43.5)	141 (31.5)	
Chemotherapy*				
None/Unknown	1262 (71.0)	915 (68.7)	347 (77.6)	<0.001[c]
Yes	516 (29.0)	416 (31.3)	100 (22.4)	

**Variable included in the propensity model. **Data not available for all subjects. Missing values: Number of lymph nodes removed = 784. Statistics presented as Mean ± SD, Median [P25, P75], N (column %). p-values: [a]Satterthwaite t-test, [b]Wilcoxon Rank Sum test, [c]Pearson's chi-square test, [d]Fisher's Exact test. BMI: body mass index; NOS: not otherwise specified; FIGO: Federation of Gynecology and Obstetrics; UNK: unknown; LVSI: lymphovascular space invasion.*

TABLE 2. Summary of treatment in low risk versus high risk groups by BMI group.

Treatment in low versus high risk subgroups				
	Low Risk Subgroup^			
Factor	Total (N = 776)	BMI <40 kg/m^2 (N = 523)	BMI ≥40 kg/m^2 (N = 253)	*p*-value
Surgery done (at least hysterectomy)				
Yes	776 (100.0)	523 (100.0)	253 (100.0)	
Lymphadenectomy				
No	474 (61.1)	303 (57.9)	171 (67.6)	
Yes	289 (37.2)	213 (40.7)	76 (30.0)	0.012[c]
Unknown	13 (1.7)	7 (1.3)	6 (2.4)	
Number of lymph nodes removed* (pelvic and/or paraaortic lymph nodes)	16.0 [9.0, 24.0]	16.0 [9.0, 24.0]	16.5 [8.0, 23.0]	0.650[b]
Radiation				
None	636 (82.0)	420 (80.3)	216 (85.4)	
Brachytherapy only	52 (6.7)	43 (8.2)	9 (3.6)	0.110[c]
External beam radiation therapy	69 (8.9)	47 (9.0)	22 (8.7)	
Other/Unknown	19 (2.4)	13 (2.5)	6 (2.4)	
Any radiation therapy				
No	636 (82.0)	420 (80.3)	216 (85.4)	0.085[c]
Yes	140 (18.0)	103 (19.7)	37 (14.6)	
Chemotherapy				
None/Unknown	750 (96.6)	503 (96.2)	247 (97.6)	0.290[c]
Yes	26 (3.4)	20 (3.8)	6 (2.4)	
	High Risk Subgroup^^			
Factor	Total (N = 1002)	BMI <40 kg/m^2 (N = 808)	BMI ≥40 kg/m^2 (N = 194)	*p*-value
Surgery done (at least hysterectomy)				
No	59 (5.9)	43 (5.3)	16 (8.2)	0.120[c]
Yes	943 (94.1)	765 (94.7)	178 (91.8)	
Lymphadenectomy				
No	271 (27.0)	203 (25.1)	68 (35.1)	
Yes	705 (70.4)	586 (72.5)	119 (61.3)	0.009[c]
Unknown	26 (2.6)	19 (2.4)	7 (3.6)	
Number of lymph nodes removed**	20.0 [13.0, 28.0]	19.0 [13.0, 28.0]	21.0 [13.0, 29.0]	0.680[b]
Radiation				
None	422 (42.1)	332 (41.1)	90 (46.4)	
Brachytherapy only	123 (12.3)	100 (12.4)	23 (11.9)	0.170[c]
External beam radiation therapy	387 (38.6)	313 (38.7)	74 (38.1)	
Other/Unknown	70 (7.0)	63 (7.8)	7 (3.6)	
Any radiation therapy				
No	422 (42.1)	332 (41.1)	90 (46.4)	0.180[c]
Yes	580 (57.9)	476 (58.9)	104 (53.6)	
Chemotherapy				
None/Unknown	512 (51.1)	412 (51.0)	100 (51.5)	0.890[c]
Yes	490 (48.9)	396 (49.0)	94 (48.5)	

*^Low Risk Subgroup: stage 1–2, low or moderate grade, <50% myometrial invasion and endometrioid type. ^^High Risk Subgroup: stage 3–4, high grade, >50% myometrial invasion, or non-endometrioid type. *Data not available for all subjects. Missing values: Number of lymph nodes removed = 487. **Data not available for all subjects. Missing values: Number of lymph nodes removed = 297. Statistics presented as Median [P25, P75], N (column %). p-values: [b]Wilcoxon Rank Sum test, [c]Pearson's chi-square test. BMI: body mass index.*

was performed in 94.1% of HR patients, with similar rates between BMI <40 kg/m^2 and ≥40 kg/m^2. As with the LR group, HR patients with BMI ≥40 kg/m^2 were significantly less likely to undergo lymphadenectomy (61.3% *vs.* 72.5%, $p = 0.009$ in HR group; 30% *vs.* 40.7%, $p = 0.012$ in LR group). Number of lymph nodes removed was similar between groups, and adjuvant radiation and chemotherapy were similar between both groups (Table 2).

Univariate and multivariable analyses assessing clinicopathologic variables and treatment effects on survival were performed (Table 3). On univariate analysis of PFS, factors associated with decreased PFS included older age (HR: 1.03, $p < 0.001$), high risk subgroup (HR: 11.8, $p < 0.001$), presence of LVSI (HR: 0.88, $p < 0.001$), and administration of chemotherapy (HR: 3.81, $p < 0.001$). On multivariable analysis, known risk factors of older age, high risk subgroup and presence of LVSI remained significant, in addition to improved PFS with performance of lymphadenectomy (HR: 0.59, $p < 0.001$). On univariate analysis, BMI ≥40 kg/m^2 indicated an improved PFS (HR: 0.66, $p = 0.008$), however, this was nonsignificant on multivariable analysis (HR: 0.89, $p = 0.49$). Adjuvant radiation therapy was found to have a protective effect on multivariable analysis (HR: 0.52, $p < 0.001$).

On univariate analysis of OS, factors associated with poorer overall survival similarly included older age (HR: 1.06, $p < 0.001$), high risk subgroup (HR: 6.70, $p < 0.001$), presence of LVSI (HR: 3.67, $p < 0.001$), and administration of chemotherapy (HR: 2.25, $p < 0.001$) (Table 3). These remained significant on multivariable analysis, with performance of lymphadenectomy also associated with improved survival (HR: 0.66, $p = 0.002$). Similar to PFS, univariate analysis for BMI ≥40 kg/m^2 indicated improved OS (HR: 0.51, $p < 0.001$), however when controlling for confounding factors on multivariable analysis, BMI ≥40 kg/m^2 was not significantly associated with OS (HR: 0.82, $p = 0.25$). With Kaplan Meier survival plot curves, PFS and OS were again similar for BMI < 40 and ≥40 kg/m^2, regardless of risk subgroup (Fig. 2).

Variables in propensity model were well balanced, and no variable met the criteria to be included as additional covariates in the final propensity-weighted Cox models (**Supplementary Table 3**). Final models show no significant difference in both PFS (HR: 0.89, 95% CI: 0.60, 1.30, $p = 0.54$) and OS (HR: 0.74, 95% CI: 0.49, 1.12, $p = 0.15$) between BMI ≥40 kg/m^2 *vs.* <40 kg/m^2 (Table 4).

4. Discussion

Obesity is associated with an increased risk of developing endometrial cancer, and multiple studies indicate worse outcomes for morbidly obese endometrial cancer patients as compared to those with normal BMI [1–10]. Clinical challenges are often encountered in the treatment of medically high-risk patients including morbidly obese patients, and it is imperative to evaluate treatment differences and outcomes in this patient population. In this study, we sought to address whether morbidly obese patients may be receiving substandard care using a large diverse cohort of endometrial cancer patients at an academic tertiary referral center. We assessed subgroups of LR and HR patients to further delineate survival differences in distinctive risk groups.

When comparing the overall population of morbidly obese patients to those BMI <40 kg/m^2, histopathologic risk factors and adjuvant treatment significantly differed between patients <40 and ≥40 kg/m^2. Morbidly obese patients' pathology was comprised of lower grade, earlier stage, <50% myometrial invasion, absent LVSI and lower risk histology. This compares favorably with other studies that similarly found obesity is associated with less aggressive histopathologic features [11, 12]. We noted that morbidly obese patients were less likely to undergo adjuvant radiation therapy and chemotherapy. This finding would initially raise concern that morbidly obese patients may receive substandard adjuvant therapy compared to non-obese patients as described in prior studies [20, 21]. However, this difference in radiation and chemotherapy administration was not seen when stratifying to LR and HR groups, suggesting that reported differences in rate of adjuvant therapy by BMI may be influenced by endometrial cancer risk group.

Although performance of surgery was found to be similar overall and between LR and HR subgroups, lymphadenectomy was undertaken significantly less frequently in the morbidly obese population both overall as well as in LR and HR subsets. When lymphadenectomy was performed, the number of lymph nodes removed in morbidly obese women was similar to non-obese women for both LR and HR groups, suggesting standard surgical technique was employed regardless of BMI. How lymphadenectomy influences endometrial cancer outcomes has been a topic of ongoing debate in the field. Prospective studies indicate no survival benefit to lymphadenectomy in early stage, low risk endometrial cancer patients [22–24]. Retrospective studies suggest a survival advantage in intermediate to high risk endometrial cancer patients undergoing complete lymphadenectomy [25, 26]. However, it is uncertain how this translates to outcomes of patients with obesity. In a study by Wissing, obese patients that were completely staged were reviewed, and pelvic lymph node positivity was found to be inversely correlated with BMI, with only 4.9% lymph node involvement in BMI ≥40 kg/m^2, compared to 18.8% lymph node involvement in BMI 30–34.9 [27]. This finding could translate to less utility for lymphadenectomy in obese patients, as we found no survival benefit in patients with BMI ≥40 kg/m^2 both in the low and the high risk subgroup despite decreased lymph node dissections. However, this finding must be interpreted with caution when considerations in the management of high risk patients are made regardless of BMI given these findings are specific to our study population, and larger studies are needed to identify the impact of lymphadenectomy on survival in morbidly obese patients.

Our robust statistical analysis indicates that BMI ≥40 kg/m^2 *vs.* <40 kg/m^2 does not confer a worse survival when controlling for adverse risk factors and treatment difference, which is in contrast to prior studies that denote a worse survival in the morbidly obese population [7, 8]. This data is supported by studies that found a similar or even favorable effect on prognosis for obese patients with endometrial cancer [11–15]. Potential differences between our study findings and other studies include differences in populations studied and

TABLE 3. Full cohort: univariate and multivariable analyses of survival outcomes for clinicopathologic and treatment variables.

Survival outcomes in clinicopathologic and treatment groups					
Univariate and multivariable analysis—Progression free survival, n = 1573*					
Variable	PFS events (n (%))	Univariate hazard ratio (95% CI)	Univariate *p*-value	Multivariable hazard ratio (95% CI)	Multivariable *p*-value
Age at diagnosis (yr)	265 (17%)	1.03 (1.02, 1.04)	<0.001	1.0120 (1.0006, 1.0236)	0.039
BMI					
BMI <40 kg/m^2	217 (18%)	Reference	-	Reference	-
BMI ≥40 kg/m^2	48 (12%)	0.66 (0.48, 0.90)	0.008	0.89 (0.65, 1.23)	0.490
Risk group					
Low risk	19 (3%)	Reference	-	Reference	-
High risk	246 (29%)	11.83 (7.42, 18.87)	<0.001	9.78 (5.90, 16.20)	<0.001
Lymphadenectomy					
None/Unknown	116 (16%)	Reference	-	Reference	
Yes	149 (17%)	1.03 (0.80, 1.31)	0.840	0.59 (0.46, 0.77)	<0.001
LVSI					
No	60 (9%)				
Yes	100 (32%)	3.88 (2.81, 5.34)	<0.001	2.01 (1.43, 2.81)	<0.001
Unknown	105 (18%)	1.90 (1.38, 2.62)	<0.001	1.61 (1.17, 2.23)	0.004
Any radiation therapy					
No	151 (16%)	Reference		Reference	
Yes	114 (18%)	1.14 (0.89, 1.45)	0.300	0.52 (0.40, 0.67)	<0.001
Chemotherapy					
None/Unknown	114 (10%)	Reference		Reference	
Yes	151 (35%)	3.81 (2.99, 4.87)	<0.001	2.09 (1.59, 2.75)	<0.001
Univariate and multivariable analysis—Overall survival, n = 1778					
Variable	OS Events (n (%))	Univariate hazard ratio (95% CI)	Univariate *p*-value	Multivariable hazard ratio (95% CI)	Multivariable *p*-value
Age at diagnosis (yr)	267 (15%)	1.06 (1.05, 1.07)	<0.001	1.04 (1.03, 1.05)	<0.001
BMI					
BMI <40 kg/m^2	227 (17%)	Reference	-	Reference	-
BMI ≥40 kg/m^2	40 (9%)	0.51 (0.37, 0.72)	<0.001	0.82 (0.58, 1.15)	0.250
Risk group					
Low risk	30 (4%)	Reference	-	Reference	
High risk	237 (24%)	6.69 (4.58, 9.79)	<0.001	5.53 (3.63, 8.41)	<0.001
Lymphadenectomy					
None/Unknown	110 (14%)	Reference	-	Reference	-
Yes	157 (16%)	1.00 (0.78, 1.28)	0.990	0.66 (0.51, 0.85)	0.002
LVSI					
No	47 (6%)	Reference	-	Reference	-
Yes	73 (21%)	3.67 (2.55, 5.30)	<0.001	2.29 (1.57, 3.34)	<0.001
Unknown	147 (21%)	2.37 (1.70, 3.31)	<0.001	2.07 (1.47, 2.89)	<0.001
Any radiation therapy					
No	143 (14%)	Reference	-	Reference	-
Yes	124 (17%)	1.18 (0.93, 1.50)	0.180	0.61 (0.47, 0.78)	<0.001
Chemotherapy					
None/Unknown	145 (11%)	Reference	-	Reference	-
Yes	122 (24%)	2.25 (1.77, 2.87)	<0.001	1.37 (1.04, 1.79)	0.023

*Statistics presented as Median (P25, P75), n (column %). p-values and Hazard Ratios: Cox Univariate Wald, Cox Multivariable Wald. *Not all patients had available recurrence information. PFS: progression free survival; CI: confidence interval; BMI: body mass index; LVSI: lymphovascular space invasion; OS: overall survival.*

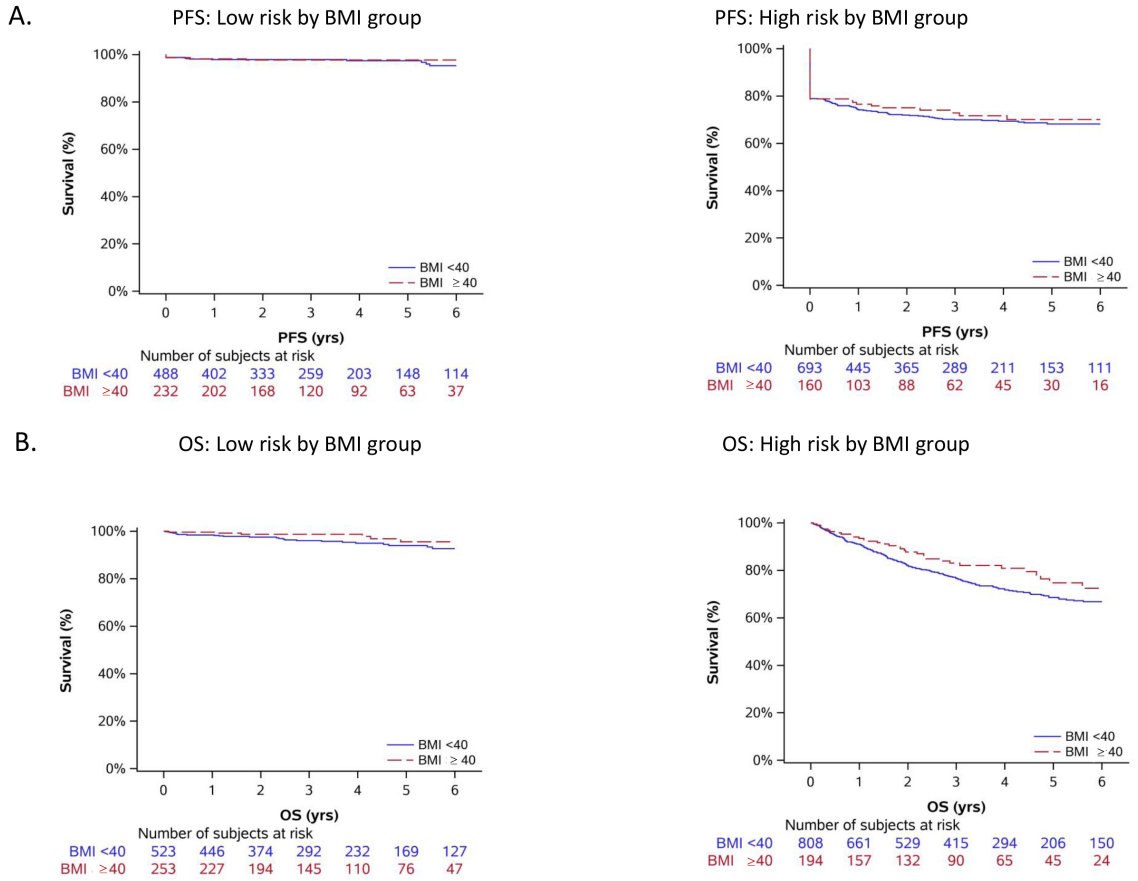

FIGURE 2. Kaplan Meier survival plots in BMI <40 kg/m^2 versus ≥40 kg/m^2 by risk groups. Comparison of (A) progression free survival and (B) overall survival between patients with BMI <40 kg/m^2 and ≥40 kg/m^2, in low risk and high risk subgroups. PFS: progression free survival; BMI: body mass index; OS: overall survival.

TABLE 4. Propensity-weighted ATT* analysis of survival outcomes for BMI <40 and ≥40 kg/m^2.

Survival outcome	Hazard ratio (95% CI)	*p*-value
PFS	0.89 (0.60, 1.30)	0.54
OS	0.74 (0.49, 1.12)	0.15

ATT: Average Effect of the Treatment, or effect from those is in group BMI ≥40 kg/m^2. The ATT weights were generated by propensity model included demographics and treatment variables, then used in the weighted univariate analyses of PFS and OS. Variables included for the propensity model are showed in Table 1 and **Supplementary Table 3 for propensity-weighting Love Plot. CI: confidence interval; PFS: progression free survival; OS: overall survival.*

confounding of underlying comorbidities. While morbidly obese patients are known to have higher rate of co-morbidities and thus elevated risk of death due to cardiovascular disease, we were not able to control for co-morbidities in our study. It is noted that while our study presents a predominantly white population, this is similar to GOG (Gynecologic Oncology Group) studies where less than 30% of patients were non-white [8]. Yet, this did not alter survival outcomes in morbidly obese patients in our study. Another hypothesized cause is due to improved care for patients with obesity related health concerns, leading to prolonged survival in previously poorly treated populations. Additionally, these morbidly obese patients are younger at diagnosis, allowing for longer life expectancy.

Limitations of the study include its retrospective nature of data collection. Furthermore, data on co-morbidities was not uniformly available for all patients and was not possible to be assessed in our study. Lymph node evaluation rate was lower than expected overall, which could lead to missed occult advanced stage disease, however, one would expect this to bias the data to represent worse survival outcomes in the morbidly obese population that underwent less lymphadenectomy, which we did not see. Additionally, sentinel lymph node mapping was not yet fully adopted during the study period from 2005–2015, and technique of lymphadenectomy was per provider preference, primarily with Mayo criteria applied for determination of risk with early stage disease [28]. Sentinel lymph node dissection in morbidly obese patients is now both feasible and widely adopted [29–31], thus rates of

lymph node dissections may differ compared to our findings. Strengths of our study include the large population size and the comprehensive statistical analysis. With propensity score weighting, a great portion of bias is eliminated while assessing a more precise treatment affect (**Supplementary Table 3**). Of note, while the sample size in this study is large, given the known excellent survival rates in low risk endometrial cancer patients, a much larger sample size is needed to find a difference in survival in this group. Future studies utilizing large population-based data could further investigate this difference.

5. Conclusions

In summary, we found that morbid obesity is correlated with improved prognostic factors. When stratifying by LR and HR disease, only surgical discrepancies in treatment were seen, with less lymphadenectomy performed in both subgroups with BMI $\geq$40 kg/m^2. However, survival outcomes remain similar in morbidly obese and non-morbidly obese patients despite this discrepancy. Future research is needed to assess the role of sentinel lymph node mapping in obese patients in relation to treatment-related outcomes, as well as potential metabolic pathways and genetic determinants that may play a role in outcomes for obese patients.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

KKCT—Study design, data analysis and primary manuscript authorship. MY—Data analysis, production of tables and figures, and contribution to methods of manuscript. MR—Data analysis and production of tables. SA—Critical review of manuscript. CMM—Critical review of manuscript. PGR—Critical review of manuscript. MMA—Significant contributions to study design, data analysis and manuscript editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study received approval by Cleveland Clinic Institutional Review Board (IRB# 17-1386). Also, this study was deemed minimal risk and waiver of informed consent was provided by Cleveland Clinic Institutional Review Board.

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CONFLICT OF INTEREST

CMM is on the Advisory Board for Clovis Oncology. The remaining authors have no relevant financial or conflicts of interest to disclose for this work.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1879416961644806144/attachment/Supplemental%20material.docx.

REFERENCES

[1] Ellison-Barnes A, Johnson S, Gudzune K. Trends in obesity prevalence among adults aged 18 through 25 years, 1976–2018. JAMA. 2021; 326: 2073–2074.

[2] Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism: Clinical and Experimental. 2022; 133: 155217.

[3] Schmandt RE, Iglesias DA, Co NN, Lu KH. Understanding obesity and endometrial cancer risk: opportunities for prevention. American Journal of Obstetrics and Gynecology. 2011; 205: 518–525.

[4] Kolano A, Pejas A, Markowiak S, Wardęszkiewicz M, Jabłońska W, Kasprzak A, *et al.* The impact of obesity on endometrial cancer: a comprehensive analysis. Journal of Education, Health and Sport. 2024; 51: 179–197.

[5] Harvey SV, Wentzensen N, Bertrand K, Black A, Brinton LA, Chen C, *et al.* Associations of life course obesity with endometrial cancer in the Epidemiology of Endometrial Cancer Consortium (E2C2). International Journal of Epidemiology. 2023; 52: 1086–1099.

[6] National Cancer Institute. SEER Cancer Stat Facts: Uterine Cancer. 2024. Available at: https://seer.cancer.gov/statfacts/html/corp.html (Accessed date: 17 July 2024).

[7] Secord AA, Hasselblad V, Von Gruenigen VE, Gehrig PA, Modesitt SC, Bae-Jump V, *et al.* Body mass index and mortality in endometrial cancer: a systematic review and meta-analysis. Gynecologic Oncology. 2016; 140: 184–190.

[8] von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma: a gynecologic oncology group study. Cancer. 2006; 107: 2786–2791.

[9] Felix AS, Sherman ME. Implications of the obesity epidemic for endometrial cancer risk, mortality, and survivorship. Gynecologic Oncology. 2021; 160: 643–645.

[10] Kokts-Porietis RL, Elmrayed S, Brenner DR, Friedenreich CM. Obesity and mortality among endometrial cancer survivors: a systematic review and meta-analysis. Obesity Reviews. 2021; 22: e13337.

[11] Anderson B, Connor JP, Andrews JI, Davis CS, Buller RE, Sorosky JI, *et al.* Obesity and prognosis in endometrial cancer. American Journal of Obstetrics and Gynecology. 1996; 174: 1171–1178; discussion 1178–1179.

[12] Münstedt K, Wagner M, Kullmer U, Hackethal A, Franke FE. Influence of body mass index on prognosis in gynecological malignancies. Cancer Causes & Control. 2008; 19: 909–916.

[13] Mauland KK, Trovik J, Wik E, Raeder MB, Njølstad TS, Stefansson IM, *et al.* High BMI is significantly associated with positive progesterone receptor status and clinico-pathological markers for non-aggressive disease in endometrial cancer. British Journal of Cancer. 2011; 104: 921–926.

[14] Bernard L, How JA, Patel S, Yates MS, Jazaeri A. Obesity is associated with improved progression-free survival in Microsatellite-Instability-High endometrial cancer treated with pembrolizumab. Gynecologic Oncology. 2024; 180: 139–145.

[15] Van Arsdale A, Miller DT, Kuo DY, Isani S, Sanchez L, Nevadunsky NS.

Association of obesity with survival in patients with endometrial cancer. Gynecologic Oncology. 2019; 154: 156–162.

[16] Slawinski CGV, Barriuso J, Guo H, Renehan AG. Obesity and cancer treatment outcomes: interpreting the complex evidence. Clinical Oncology. 2020; 32: 591–608.

[17] Thimotheo Batista JP, Santos Marzano LA, Menezes Silva RA, de Sá Rodrigues KE, Simões E Silva AC. Chemotherapy and anticancer drugs adjustment in obesity: a narrative review. Current Medicinal Chemistry. 2023; 30: 1003–1028.

[18] Ramadan B, Dahboul H, Mouawad C, Aoun R, Kassar S, Kassouf E, *et al.* Obesity: a risk factor for postoperative complications in laparoscopic surgery for colorectal cancer. Journal of Minimal Access Surgery. 2024; 20: 12–18.

[19] Agnew HJ, Kitson SJ, Crosbie EJ. Gynecological malignancies and obesity. Best Practice & Research Clinical Obstetrics & Gynaecology. 2023; 88: 102337.

[20] Uccella S, Bonzini M, Palomba S, Fanfani F, Ceccaroni M, Seracchioli R, *et al.* Impact of obesity on surgical treatment for endometrial cancer: a multicenter study comparing laparoscopy *vs.* open surgery, with propensity-matched analysis. Journal of Minimally Invasive Gynecology. 2016; 23: 53–61.

[21] Javaid S, Frasier K, Chaudhary AJ. Impact of obesity on in-hospital mortality and morbidity among patients admitted for antineoplastic chemotherapy: a nationwide analysis. Clinical and Translational Oncology. 2024; 26: 977–984.

[22] ASTEC study group; Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. The Lancet. 2009; 373: 125–136.

[23] Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, *et al.* Systematic pelvic lymphadenectomy *vs.* no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. Journal of the National Cancer Institute. 2008; 100: 1707–1716.

[24] Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database of Systematic Reviews. 2017; 10: CD007585.

[25] Swift BE, Philp L, Atenafu EG, Malkani N, Gien LT, Bernardini MQ. Lymphadenectomy for high-grade endometrial cancer: does it impact lymph node recurrence? European Journal of Surgical Oncology. 2022; 48: 1181–1187.

[26] Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. The Lancet. 2010; 375: 1165–1172.

[27] Wissing M, Mitric C, Amajoud Z, Abitbol J, Yasmeen A, López-Ozuna V, *et al.* Risk factors for lymph nodes involvement in obese women with endometrial carcinomas. Gynecologic Oncology. 2019; 155: 27–33.

[28] Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? American Journal of Obstetrics and Gynecology. 2000; 182: 1506–1519.

[29] Werner S, Gadomski T, Pereira E, Jeannine V. Lymphatic mapping and obesity with sentinel lymph node biopsy in endometrial cancer. Gynecologic Oncology. 2021; 162: S202.

[30] Fennimore NJ, Fitch K, Kiff J, Nguyen CG, Garg B, Munro EG, *et al.* Success rates of sentinel lymph node mapping for endometrial cancer in patients with body mass index <45 compared with body mass index ≥ 45. Journal of Minimally Invasive Gynecology. 2023; 30: 735–741.

[31] Matanes E, Eisenberg N, Amajoud Z, Gupta V, Yasmeen A, Ismail S, *et al.* Sentinel lymph node sampling as an alternative to lymphadenectomy in patients with endometrial cancer and obesity. Journal of Obstetrics and Gynaecology Canada. 2021; 43: 1136–1144.e1.

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